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THE USE OF N^{15} COMPOUNDS IN DETERMINING ORGANIC STRUCTURES AND MECHANISMS

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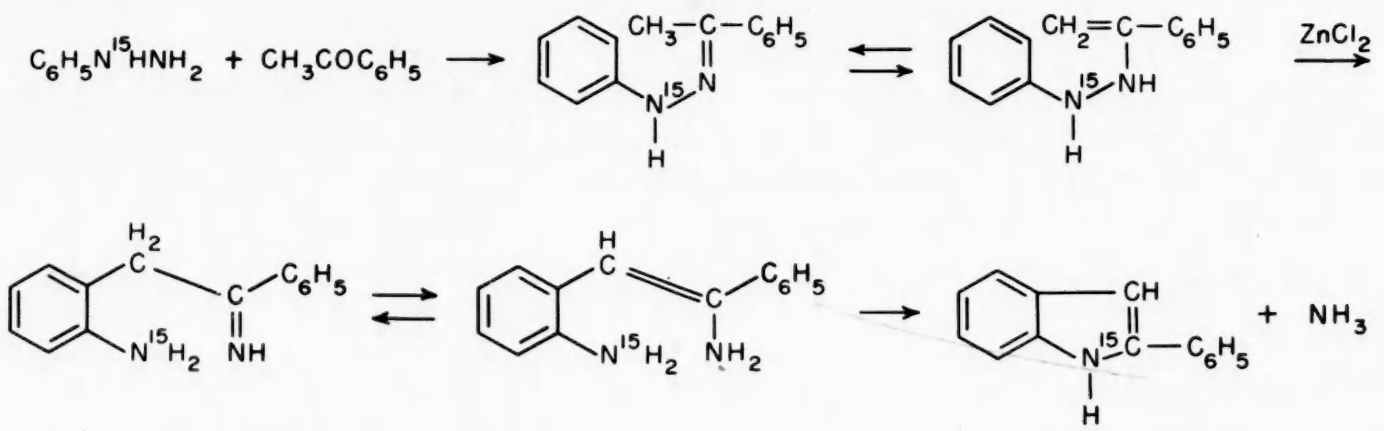
The remarkable progress made in organic chemistry during the past thirty years has solved a great many problems of long standing dealing with nitrogenous substances. The principal ones are certain cyclizations in which one of the two nitrogen atoms originally present is eliminated, the structure of the aliphatic diazo group, the azide group, and some decompositions and rearrangements. By the use of substances containing the N^{15} isotope, considerable progress has been made in their solution. Some mechanisms have been established, and the correct one of several isomeric structures has been pointed out in many instances. Other applications have been found useful, as will appear in this survey.

Many problems in organic chemistry, in which the use of the N^{15} isotope can be a valuable aid, are still awaiting solution. Among these are debatable mechanisms, rearrangements, and reaction kinetics. The use of N^{15} is of great value to the biochemist in determining biological functions and reactions.

Ring Closures

Perhaps the earliest utilization of N^{15} was its application by Allen and Wilson (1) to the Fischer indole synthesis from phenylhydrazine. Their work showed that the only acceptable mechanism of ring closure was that advanced a decade previously by Robert Robinson. The authors made use of α-labeled phenylhydrazine, $C_6H_5N^{15}HNH_2$, from which α-phenylindole, still containing the heavy nitrogen, resulted.



This mechanism was recently confirmed through the work of Clusius (2), who prepared α-methylindole from β-labeled phenylhydrazine, $C_6H_5NHN^{15}H_2$; in this instance, the isotopic nitrogen was evolved as $N^{15}H_3$.

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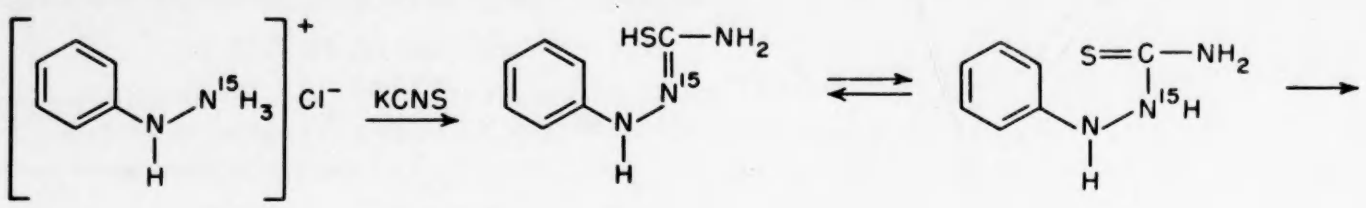
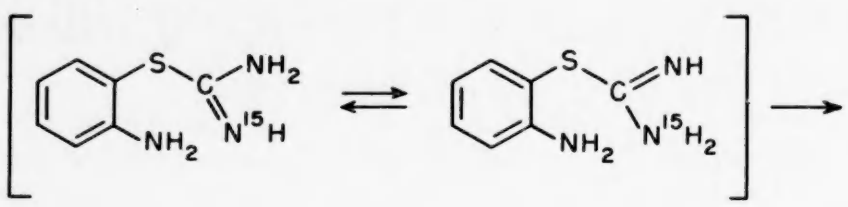
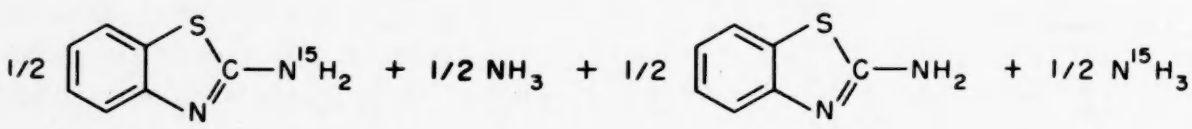
According to Clusius, the isotopic distribution in the synthesis of 2-aminobenzothiazole from 1-phenylthiosemicarbazide (2) with β-labeled phenylhydrazine is an even more convincing argument in favor of an ω,ω'-diamine intermediate. At the reaction temperature of 130° C., a tautomeric equilibrium is rapidly taking place as the ring closure occurs, and, since the cyclization occurs with both tautomeric forms, the end products are always formed in equal proportions.

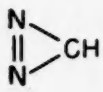
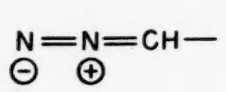


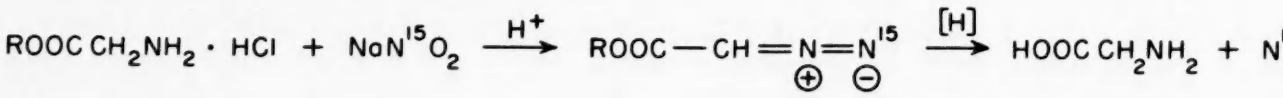




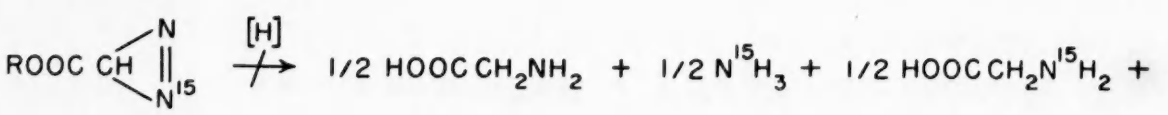
Traube's uric acid synthesis is also analogous (3). When uric acid is prepared from 4,5-diaminouracil and N^{15} urea, *all* of the ammonia liberated comes from the labeled urea while the amino groups of the uracil are quantitatively converted to the imidazole ring of the acid. Cavalieri (3) studied the preparation of uric acid from uramil and N^{15} urea, and from 4,5-diaminouracil. By means of the labeled uric acid thus prepared, he studied the mechanism of oxidative cleavage of uric acid in three ways, i.e., with alkaline potassium permanganate, nitric acid, and chlorine.

Structure of Aliphatic Diazo Compounds

Whether ethyl diazoacetate (and other aliphatic diazo compounds) exists as a ring  or open chain  has been debated for many years. When the ester was prepared from glycine ester hydrochloride and labeled sodium nitrite, and the ethyl diazoacetate was reduced to glycine and ammonia, the isotopic distribution supported the case of the chain by the formation of glycine and heavy ammonia (4).



Had the ester existed as the ring form, the two almost identical C–N^{14} and C–N^{15} bonds would have been broken and the following isotopic distribution would have been expected:



Structure of Azides

Before considering organic azides, the azide ion itself merits consideration. Curtius's concept that the azide ion existed as a ring stood for eighty years, while that of others, such as Thiele-Angeli, assumed a chain form. By means of N^{15}, its definite structure has been determined. Labeled hydrazoic acid, $HNNN^{15}$ (5), was prepared from heavy ethyl nitrite and hydrazine hydrate in the presence of potassium methoxide, according to Thiele-Stolle. The labeled acid was subjected to extensive reduction and oxidation reactions. From the isotopic examination of the various reaction products, it was proved that the linear structure of the azide ion was the only possible configuration. The isotopic labeling distinguished the central nitrogen

$\left[\overset{\ominus}{N}=\overset{\oplus}{N}=\overset{\ominus}{N^{15}}\right]^-$ from the end atoms of the azide ion.

The organic azide, $C_6H_5NNN^{15}$, was synthesized from ordinary phenylhydrazine and labeled nitrous acid (6). Unexpectedly, it was found that the reaction proceeded by at least two paths, since not only $C_6H_5NNN^{15}$ but also some $C_6H_5NN^{15}N$ was found. It appears, therefore, that both α- and β-nitrosophenylhydrazine are intermediates in the reaction. The percentages of the α- and β-isomers depended greatly

$$C_6H_5NHNH_2 + HN^{15}O_2 \xrightarrow{0°C} \begin{cases} \left[C_6H_5-N(N^{15}O)-NH_2\right] \xrightarrow{2\%} C_6H_5N=\overset{\oplus}{N^{15}}=\overset{\ominus}{N} \\ \left[C_6H_5NHNHN^{15}O\right] \xrightarrow{98\%} C_6H_5N=\overset{\oplus}{N}=\overset{\ominus}{N^{15}} \end{cases}$$

upon the diazotization temperature.

Two labeled phenyl azides, $C_6H_5N^{15}=\overset{\oplus}{N}=\overset{\ominus}{N}$ and $C_6H_5N=\overset{\oplus}{N^{15}}=\overset{\ominus}{N}$, were prepared so that the three nitrogen atoms were joined together in a definite structural order, using benzenediazonium perbromide (7); this reaction gives an isotopically pure product. The equations illustrated below are for the phenyl azide, $C_6H_5N^{15}=N=N$.

$$\underset{①}{C_6H_5N^{15}H_2}\cdot HCl + \underset{②}{HNO_2} \longrightarrow \left[C_6H_5-\underset{①}{N^{15}}\equiv\underset{②}{N}\right]^+Cl^- + Br_3^- \longrightarrow$$

$$\left[C_6H_5-N^{15}\equiv N\right]^+Br_3^- \xrightarrow{\underset{③}{4NH_3}} \underset{①}{C_6H_5N^{15}}=\underset{②}{\overset{\oplus}{N}}=\underset{③}{\overset{\ominus}{N}} + \underset{③}{3NH_4Br}$$

The labeled phenyl azide was decomposed with hydrochloric acid to *p*-chloroaniline and nitrogen. The conversion of the phenyl azide into diazoaminobenzene was

$$C_6H_5N^{15}=\overset{\oplus}{N}=\overset{\ominus}{N} \xrightarrow{HCl} ClC_6H_5N^{15}H_2 + N\equiv N$$

accomplished with phenylmagnesium bromide, and the complete reduction of the labeled diazoaminobenzene gave aniline and ammonia. Isotopic analyses of the

$$C_6H_5N^{15}=\overset{\oplus}{N}=\overset{\ominus}{N} \xrightarrow[H_2O]{C_6H_5MgBr} C_6H_5N^{15}=N-NHC_6H_5 \xrightarrow{[6H]}$$

$$C_6H_5N^{15}H_2 + NH_3 + C_6H_5NH_2$$

reaction products were made at each step in these reactions. The isotopic, labeled

phenyl azide, $C_6H_5N{=}\overset{\oplus}{N}{}^{15}{=}\overset{\ominus}{N}$, was prepared from ordinary aniline and labeled nitrous acid. Similar reactions to those illustrated were performed, except that the labeled nitrogen atom *is* found on the central nitrogen of the azide ion. Results showed that the nitrogen atoms in phenyl azide can only be linear. The assumption of the ring form should therefore be abandoned permanently from any further discussion.

Phenyl azide was prepared from benzenediazonium salts and phenylhydrazine salts in mineral acid solution. Through labeling with N^{15}, it was found that this reaction proceeded in two ways, as in the equation below, probably through a tetrazine

$$\left[C_6H_5N^{15}{\equiv}N\right]^+ + H_2NNHC_6H_5 \xrightarrow{H^+} \left[C_6H_5N^{15}{=}N{-}NH{-}NH{-}C_6H_5\right]$$

$$\swarrow \qquad \searrow$$

$$C_6H_5N^{15}NN + H_2NC_6H_5 \qquad C_6H_5N^{15}H_2 + NNNC_6H_5$$

intermediate (8). The reaction temperature greatly influenced the distribution of products isolated.

Decomposition Reactions

Phenylhydrazine was decomposed by distillation under atmospheric pressure in the presence of copper salts in a hydrogen atmosphere, according to the equation given by Clusius (9). This is one of the few reactions in which an aromatic carbon–nitrogen bond is broken.

$$2C_6H_5NHN^{15}H_2 \longrightarrow C_6H_5NH_2 + N{\equiv}N^{15} + N^{15}H_3 + C_6H_6$$

Labeled N,N-diphenylhydrazine decomposed according to the reaction (9):

$$3(C_6H_5)_2N{-}N^{15}H_2 \xrightarrow{270°C} 3(C_6H_5)_2NH + N_2^{15} + N^{15}H_3 .$$

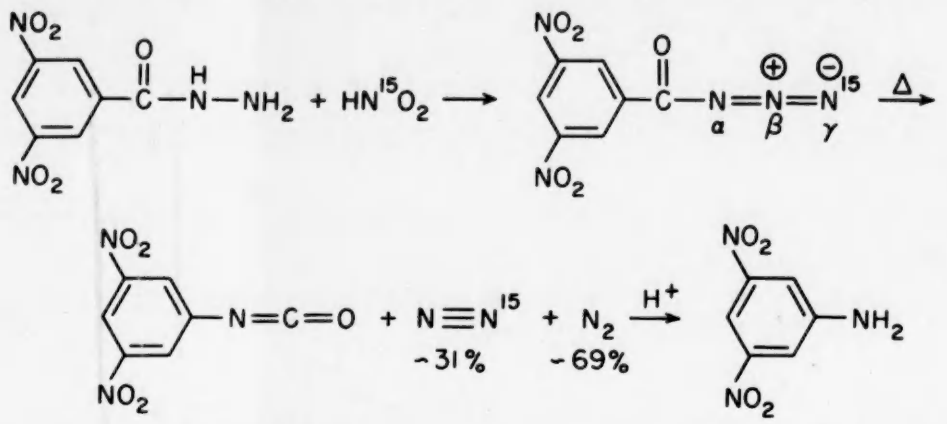
In this case, the strong carbon-nitrogen bond was not broken. The cracking mechanism proposed for the reaction involved the $(C_6H_5)_2$–N, $N^{15}H_2$, and $(C_6H_5)_2$-–N–$N^{15}H$ radicals in a four-step chain reaction.

The thermal decomposition of labeled hydrazobenzene to azobenzene has been studied by Holt (10), who established that the disproportionation involved no fission of the N–N bond. The photochemical decomposition of labeled hydrazobenzene to azobenzene was also studied and the mechanism is thought to be similar to the thermal decomposition.

Rearrangements

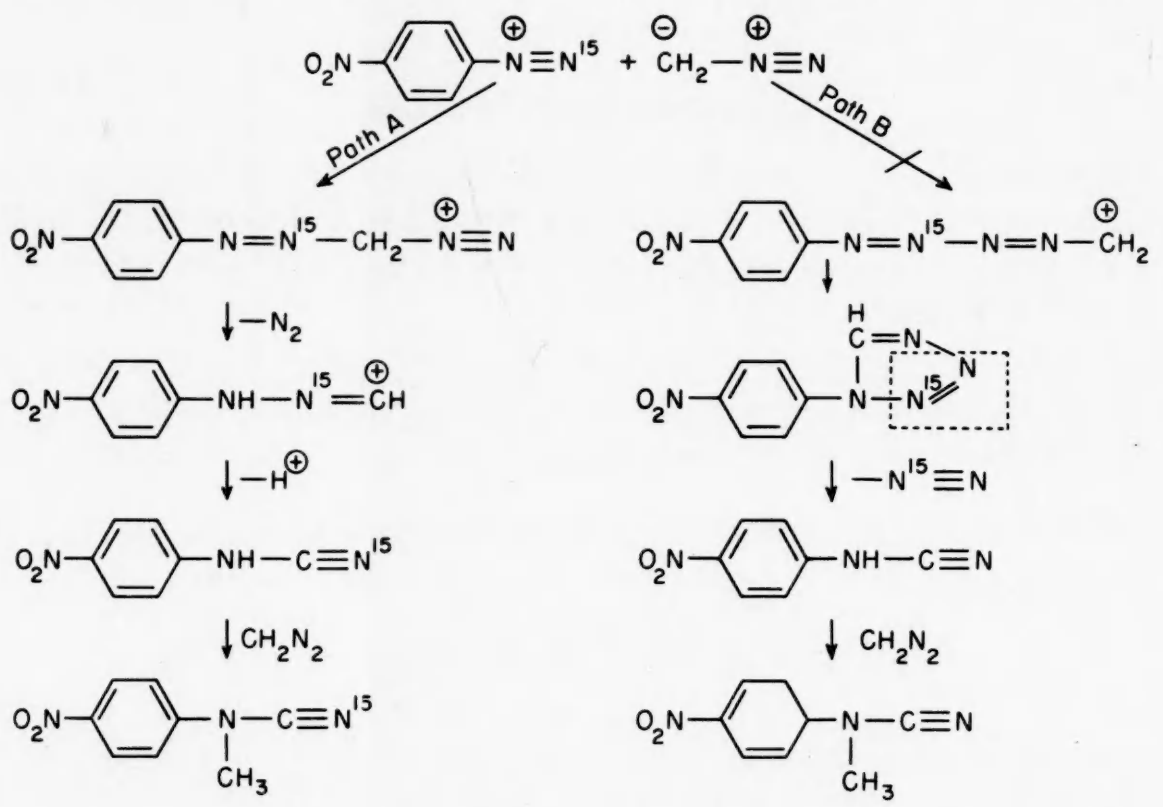
The Curtius rearrangement of 3,5-dinitrobenzazide has also been examined (11). The labeled azide was prepared from 3,5-dinitrobenzhydrazide and labeled nitrous acid. Thermal decomposition of the azide gave heavy nitrogen, and, upon hydrolysis,

normal 3,5-dinitroaniline. This finding confirms the currently accepted mechanism of rupture of the α,β-nitrogen bond, followed by the elimination of nitrogen. These



results eliminate any possibility of a cyclic intermediate, or intermolecular exchanges of azide ion.

In the preparation of N-methyl-*p*-nitrophenylcyanamide (12) from excess diazomethane and labeled *p*-nitrobenzenediazonium chloride, it appears probable that the nitrile may have resulted through a new type of sextet rearrangement of carbonium ions, as in Path A. Another possibility of the nitrile having formed through a tetra-



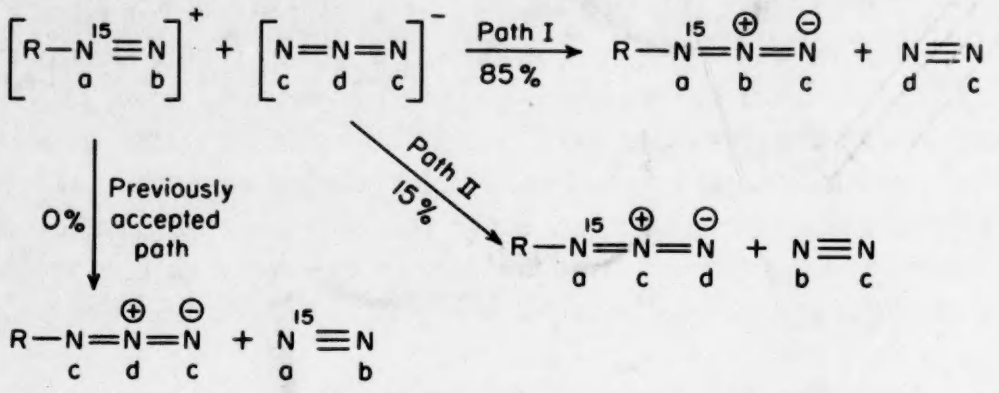
zole intermediate along Path B was discarded, since all of the heavy nitrogen was found in the cyano group of the end product.

Miscellaneous Reactions

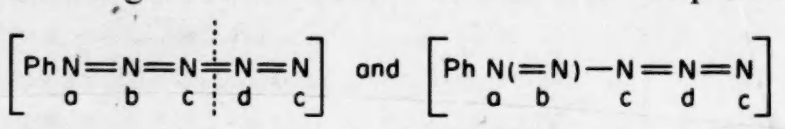
Interesting and completely unexpected results were obtained when a diazonium salt was allowed to react with azide ion to give phenyl azide and nitrogen (13). While the expected mechanism would involve the loss of nitrogen from the diazonium ion just as nitrogen is lost from the diazonium ion in the formation of aryl halides in the presence of halide ion, a study of the mechanism with labeled nitrogen showed that this was not the case.

To study the mechanism of this reaction, three experiments were carried out in which the nitrogen atoms, a, b, and c, were labeled in the respective positions shown

below. The experiment in which the nitrogen was labeled in the "a" position is illustrated in the reaction scheme. Isotopic analysis of this experiment, combined with



the reactions in which the labeled nitrogen was in positions "b" and "c," showed that Path I and Path II were followed. The reaction did not occur as expected, but probably proceeded through the formation of the unstable pentazines.



Proof of the nitrate ion in liquid nitrogen tetraoxide has been demonstrated in the following manner by Clusius (14): If labeled tetramethylammonium nitrate, $(CH_3)_4NN^{15}O_3$, is dissolved in anhydrous liquid nitrogen tetraoxide, a quantitative exchange of the nitrate ion occurs with the solvent. Since ordinary quaternary ammonium salt is isolated, it is concluded that, in order for the exchange to have occurred, the liquid nitrogen tetraoxide must contain some nitrosyl nitrate, $NO{\cdot}NO_3$, which dissociates into the ion-pair, $NO^+{\cdot}NO_3^-$, and the free ions, NO^+ and NO_3^-.

References

1. Allen, C. F. H., and Wilson, C. V., *J. Am. Chem. Soc.*, 65, 611-612 (1943).
2. Clusius, K., and Weisser, H. R., *Helv. Chim. Acta*, 35, 400-406 (1952).
3. Cavalieri, L. F., Blair, V. E., and Brown, G. B., *J. Am. Chem. Soc.*, 70, 1240-1242 (1948).
   Cavalieri, L. F., and Brown, G. B., *Ibid.*, 70, 1242-1243 (1948).
   Clusius, K., and Vecchi, M., *Helv. Chim. Acta*, 36, 1324-1326 (1953).
4. Clusius, K., and Lüthi, U., *Chimia*, 8, 96 (1954).
5. Clusius, K., and Hürzeler, H., *Helv. Chim. Acta*, 36, 1326-1332 (1953).
6. Clusius, K., and Weisser, H. R., *Ibid.*, 35, 1548-1559 (1952).
7. Clusius, K., and Hürzeler, H., *Ibid.*, 37, 383-388 (1954).
8. Clusius, K., and Craubner, H., *Ibid.*, 38, 1060-1065 (1955).
9. Clusius, K., and Hoch, M., *Ibid.*, 33, 2122-2127 (1950).
   Clusius, K., and Vecchi, M., *Ibid.*, 36, 933-937 (1953).
10. Holt, P. F., and Hughes, B. P., *J. Chem. Soc. (London)*, pp. 1666-1669 (1953); *Ibid.*, pp. 98-100 (1955).
11. Bothner-By, A. A., and Friedman, L., *J. Am. Chem. Soc.*, 73, 5391-5392 (1951).
12. Huisgen, R., and Koch, H. J., *Naturwissenschaften*, 41, 16 (1954).
    Clusius, K., Hürzeler, H., Huisgen, R., and Koch, H. J., *Ibid.*, 41, 213 (1954).
    Clusius, K., *Angew. Chem.*, 66, 497-506 (1954).
13. Clusius, K., and Hürzeler, H., *Helv. Chim. Acta*, 37, 798-804 (1954).
14. Clusius, K., and Vecchi, M., *Ibid.*, 36, 930-933 (1953).

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